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NEWLY FDA-APPROVED DRUGS AND BIOLOGIC (JANUARY-DECEMBER 2005) PART 1

The aim of this review is to survey the new "molecular entities" (NME) drugs and new biological license applications (BLA) approved by the Food and Drug Administration (FDA) in the year 2005 (i.e., those not previously marketed in the United States of America).

In Part 1 some of the drugs subject to "Priority Review" (i.e., those representing significant improvements compared with marketed products [1]) and the BLA [6 NME and 2 BLA, 29 references] will be considered. As for the drugs subject to "Standard Review" (i.e., those having therapeutic qualities similar to those of already marketed products [1]) (5 NME), only basic information (product, sponsor, date approved, indication, structural formula and availability in Italy) will be given [2]. Part 1 of the review follows the reviews about NME approved by the FDA in the years 1998-2003, and NME and BLA approved in 2004 [3].

New Molecular Entities and Biological License Applications Approved in 2005 with Priority Review. Part 1

In order to offer an overview of the subject, the drugs have been divided into therapeutic classes, as can be seen in Fig. 1. Antiviral (as in 1998-2002) and antitumor drugs are present (as in 1998-2004), because of the great interest in the related diseases. In addition enzymes (as in 2004), growth factors, immunomodulatories, an antifungin (as in 2001), an antibiotic (as in 1999, 2000), a chelating (as in 2004) and an anti-inflammatory (as in 1998-2000) drug are included in the FDA-approved NME and BLA. In Part 1 anti-inflammatory, immunomodulatory agents, growth factors and enzymes are reported.

Anti-inflammatory drugs

Nevanac™ (Alcon)
Nepafenac, opthalmic suspension 0.1% [4]
Indication: nonsteroidal anti-inflammatory (NSAIDs) prodrug of amfenac for treatment of pain and inflammation associated with cataract surgery.
Date approved: 19-08-2005

Decreasing of central vision after cataract surgery is a frequent event often caused by cystoid macular edema (CME), a condition consisting in the accumulation of fluid in the central retina, probably due to irritation and inflammation related to surgery [5].The treatment of a variety of ophthalmic inflammatory conditions with topical NSAIDs has been gaining acceptance [5]. In the anterior chamber, NSAIDs have been shown to decrease post-operative inflammation, and to reduce pain and discomfort following surgery; however, the anti-inflammatory effectiveness of NSAIDs in the posterior segment is less clear [5]. The ideal topical NSAID would have excellent anti-inflammatory and analgesic properties, be non-toxic to the cornea, and confortable for the patient; it would reduce inflammatory cell and flare reaction in the acqueous humor, penetrate target intraocular tissues at thera-

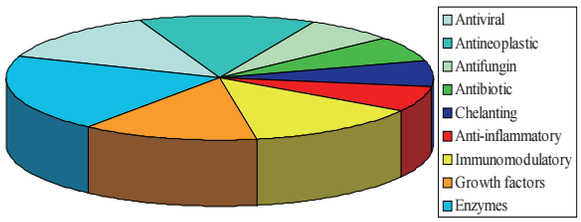

Fig. 1 - Therapeutic classes of NME and BLA approved by "priority review"

peutic levels, and prevent CME in the posterior segment [5].

Nepafenac (**1**, Fig. 2), an arylacetic acid derivative synthesized as described in [6], is a NSAID pro-drug having properties similar to those for the ophthalmic formulations of bromfenac, diclofenac, and ketorolac, the other NSAIDs for use in the examined therapy, blocking the synthesis of prostaglandins (PGs) by inhibiting the cyclooxygenase cascade [5, 7]. Compared to conventional NSAIDs, when entering the anterior chamber, **1** permeates in a faster time as it is a neutral molecule, thus increasing biodistribution and intraocular efficacy [5, 8]; successively, **1** is rapidly converted to a potent NSAID amfenac, by intraocular tissue hydrolases, reducing the risk of surface complications because the active drug does not accumulate in the cornea and ocular surface tissues [5, 9]. In addition, **1**'s ability to inhibit PG synthesis in the retina/choroid following topical administration indicates the drug also targets suppression of PG synthesis in the posterior segment [5, 8, 10, 11]. Finally, treatment with **1** begins one day prior to surgery, on the contrary to other NSAIDs, with which it is initiated 24 hours after surgery [7].

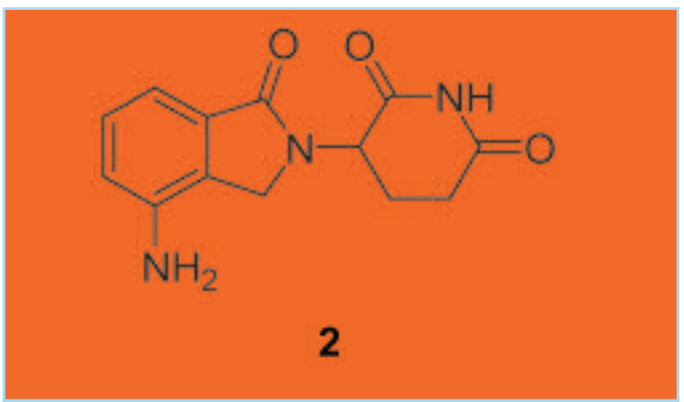

Fig. 3 - Immunomodulatory drugs

Immunomodulatory drugs

Revlimid® (Celgene) (orphan drug)

Lenalidomide, 5, 10, 15 & 25 mg, capsule [12]

Indication: immunomodulatory drug for treatment of patients with transfusion dependent anemia due to low or intermediate-**1** risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Date approved: 27-12-2005

MDS constitute a heterogeneous group of clonal stem cell disorders characterized by ineffective haematopoiesis, cytopenia, bone marrow dysplasia, and a risk of progression to acute myeloid leukemia (AML) [13]. MDS is classified largely on the basis of cellular morphology and comprises various categories

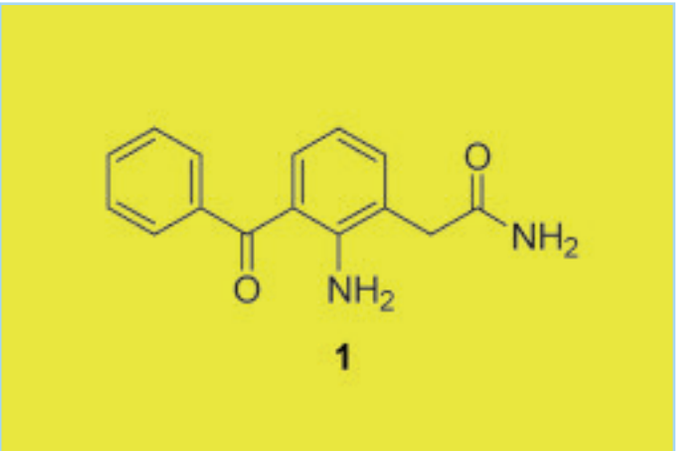

Fig. 2 - Anti-inflammatory drugs

including RA, RARS, RAEB-T, CMcL and more recently one subtype with specific cytogenetics, the 5q-syndrome [13, 3g]. Progenitor apoptosis in MDS may have intrinsic and extrinsic mechanisms, with the latter including T-cell mediated bone marrow failure, for which antithymocyte globulin treatment may be effective, as well as negative effects caused by the marrow microenvironment [13]. Elevated levels of tumor necrosis factor (TNF)-α mRNA and protein have been demonstrated in bone marrow mononuclear cells from MDS patients but also angiogenesis, T-cell-mediated failure or other factors are involved in MDS [13]. At present, the primary potentially curative treatment of MDS is allogenetic stem-cell transplantation or other forms [13] including the administration of azacitidine, the first drug approved in therapy for the disease [3g, 14, 15].

Lenalidomide (**2**, Fig. 3), a 4-aminoglutarimide analogue of thalidomide synthesized as reported in [16], acts with a mechanism that remains to be fully characterized but is thought to be similar to that proposed for thalidomide, such as inhibition of TNF-α, endothelial cell production and angiogenesis, or stimulation of T-cells [12c, 17]. **2** presents the advantage of an oral administration versus the subcutaneous injection required with azacitidine [18], and a better pharmacological profile in comparison to thalidomide but, due to its structural similarities, is contraindicated in pregnant women and women capable of becoming pregnant [12c, 19]. More recently, **2** received a new claim for use in combination with dexamethasone for treatment of multiple myeloma patients who have received at least one prior therapy [20].

Growth factors

Increlex™ (Tercica) (orphan drug)

Mecasermin (rDNA origin), 0.04-0.08 mg/mL, injection [21]

Date approved: 30-08-2005

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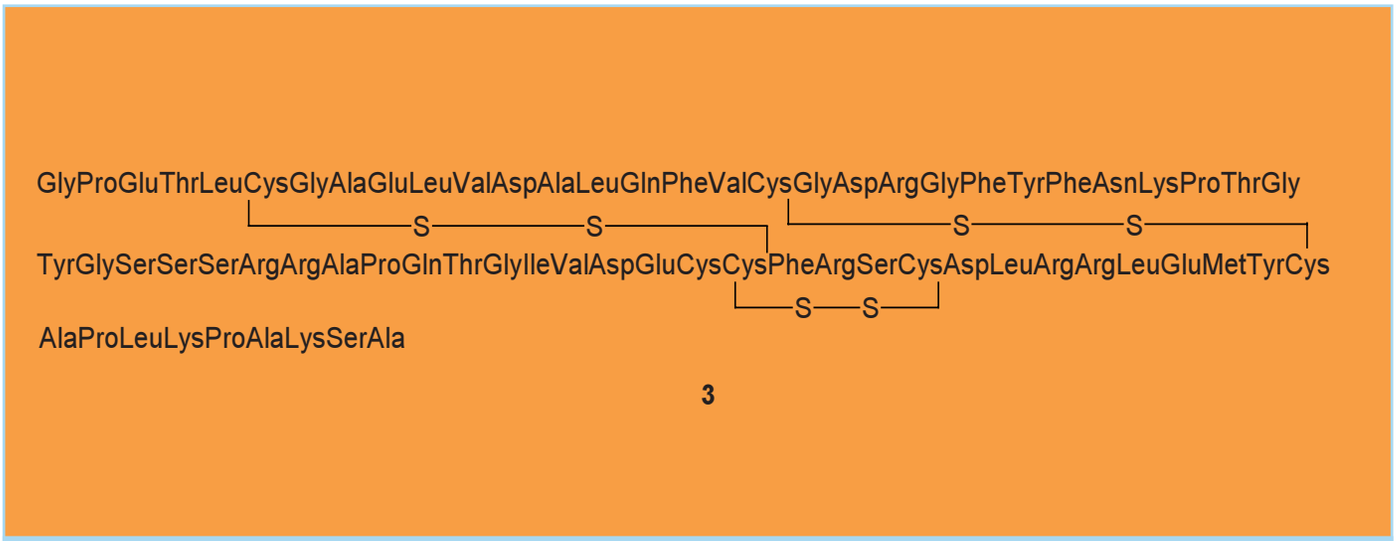

Fig. 4 - Growth factors

iPlex™ (formerly *SomatoKine*) (Insmed) (orphan drug)
Mecasermin rinfabate (rDNA origin), 36 mg/mL, injection [22]
Date approved: 12-12-2005

Indication: recombinant human insulin-like growth factor (rhIGF)-1, and rhIGF-1 binding protein-3 complex (IGFBP-3) in the case of rinfabate, for treatment of growth failure in children with severe primary IGF-1 deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

IGF-1, also known as somatomedin C, is structurally and functionally related to insulin but exerts greater growth-promoting and anabolic effects [21]. At normal plasma levels, IGF-1 has a growth-promoting effect while elevated concentrations can have anabolic effects or produce hypoglycemia, with some of its effects modulated by the presence or absence of different IGF-binding proteins (IGFBPs) [21]. IGF-1 is a key factor in GH-resistant individuals of idiophatic short stature, leading to the rare inherited conditon of primary IGFD referred to as Laron Syndrome [21]. IGF-1 also has effects on bone mineral density and has been shown to encourage osteoblast production that can precede new bone formation [21].
Mecasermin (**3**, Fig. 4) and mecasermin rinfabate (**4**, [22a]) are produced by two separate *E. coli* strains: one containing the human gene for IGF-1, the other that for IGFBP-3 [22a]. The pharmacological effects of **3** in children are the promotion of linear growth and, secondly, insulin sensitization, and insulin-like effects [22a]. There are no known direct GH-promoting effects of IGFRB-3, the primary effect of IGFRB-3 in **4** being the modulation of IGF-1 action [22a]. For the treatment of IGF-1 deficiency, it is desirable to administer IGF-1 bound to IGFBP-3 to maintain the normal equilibrium of these proteins in the blood [22b]. **4** mimics the effects of the natural protein complex in the bloodstream and appears to augment the natural supply of these linked compounds [22b].

Enzymes

Hydase™ (PrimaPharm)
Bovine hyaluronidase, USP 150 IU/mL, injection [23a]
Date approved: 25-10-2005

Hylenex™ (Tercica)
Human recombinant hyaluronidase, USP 150 IU/mL, injection [23b]
Date approved: 02-12-2005

Indications: bovine/human recombinant hyaluronidase adjuvant to increase absorption and dispersion of other injected drugs; for hyperdermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Hyaluronidase is a spreading or diffusing substance which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intracellular ground substance of connective tissue, and of certain specialized tissue. Hyaluronidase acts by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glu-

curonic acid [23, 3g]. This temporarily decreases the viscosity of the cellular cement and promotes diffusion of injected fluids or of localized transudates or exudates, thus facilitating their absorption [23, 3g]. Hyaluronidase cleaves glycosidic bonds of hyaluronic acid and causes rapid spreading and provides local interstitial pressure adequate to furnish the necessary mechanical impulse [23, 3g]. Bovine hyaluronidase (**5**) is a preparation of purified testicular derivation [23a], whereas human recombinant type (**6**) is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20) [23b].

New Biological License Applications Approved in 2005

Naglazyme™ (BioMarin) (orphan drug)
Galsulfase (formerly *Aryplase*), 1 mg/mL, injection [24]

Indication: I.V. enzyme replacement therapy for mucopolysaccharidosis (MPS) VI.
Date Approved: 31-05-2005 (priority review) (available also in Italy [25])

MPS type VI (Maroteaux-Lamy syndrome) is an lysosomal storage disorder (LSD) caused by the deficiency of *N*-acetylgalactosamine-4-sulfatase, the enzyme responsible for the catabolism of glycosaminoglycan (GAG) [24a,c-e]. The accumulation of GAG substrate leads to excessive amounts of dermatan sulfate with progressive diseases such as multiple skeletal deformities, and organ and soft tissue involvement [24a,c]. For several years the treatment option available for LSD was surgical intervention or bone-marrow transplantation; only recently, it was demonstrated that replacement of the deficient enzyme involved in that pathology could successfully treat the disease [24a,d].
Galsulfase (**7**) is a normal variant form of the polymorphic human enzyme *N*-acetylgalactosamine-4-sulfatase, produced by recombinant DNA technology in a Chinese hamster ovary cell line [24e]. 7 comprises 495 amino acids (AAs) and contains six asparagine-linked glycosylation sites four of which carry a bis mannose-6-phosphate mannose, an oligosaccharide for specific cellular recognition [24e]. Post-translational modification of Cys53 residue produces the catalytic AA residue Cα-formylglycine, which is required for enzyme activity [24e].
Orencia™ (Bristol-Myers Squibb)
Abatacept, 250 mg, injection [26]

Indication: T-cell co-stimulation modulator for treatment of adults with moderately to severely active rheumatoid arthritis (RA), for reducing signs and symptoms, including major clinical response, slowing the progression of structural damage, and improving physical function in patients who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), such as metotrexate or a TNF antagonist.
Date Approved: 23-12-2005 (priority review)

RA is a chronic inflammatory autoimmune disorder characterized by symmetrical joint inflammation, often accompanied by extra-articular disease or systemic effects, mediated by the activation of T-cells [26a]. This event results in the production of cytokines and the regulation of downstream immune responses, and involves both the interaction of major histocompatibility complex-bound antigen with the T-cell receptor and a number of co-stimulatory molecules, non-antigen specific but necessary for T-cell activation [26c]. In the absence of this co-stimulatory signal, a state of T-cell energy is produced in which T-cell are functionally inactivated or hyporesponsive [26a]. Treatment options include NSAIDs, corticosteroids, traditional nonbiological DMARDs (including metrotexate) and, more recently, biological DMARDs (e.g. anti-TNF therapy) [26b,d, 27]. However, some problems related to deterioration in radiographs and joint function or a proportion of patients who do not respond to therapy indicates the need for improved therapies [26b, 28].
Abatacept (**8**), produced by recombinant DNA technology in a mammalian cell expression system, is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to modified Fc (hinge, CH_2, and CH_3 domains) portion of human immunoglobulin G1 (lgG1) [26f]. 8 acts as a selective costimulation modulator inhibiting T-lymphocyte activation by binding to CD80 (B7-1) and CD86 (B7-2) ligands on the antigen-presenting cells (APCs), thereby blocking the interaction of these molecules with CD28 on T-cells, which is thought to be important in the pathogenesis of RA [26f,e,b, 29].

New Molecular Entities Approved in 2005 with Standard Review

Byetta® (Amylin/Lilly)
Exenatide, 5 & 10 mg, injection
Indication: incretin mimetic for adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking

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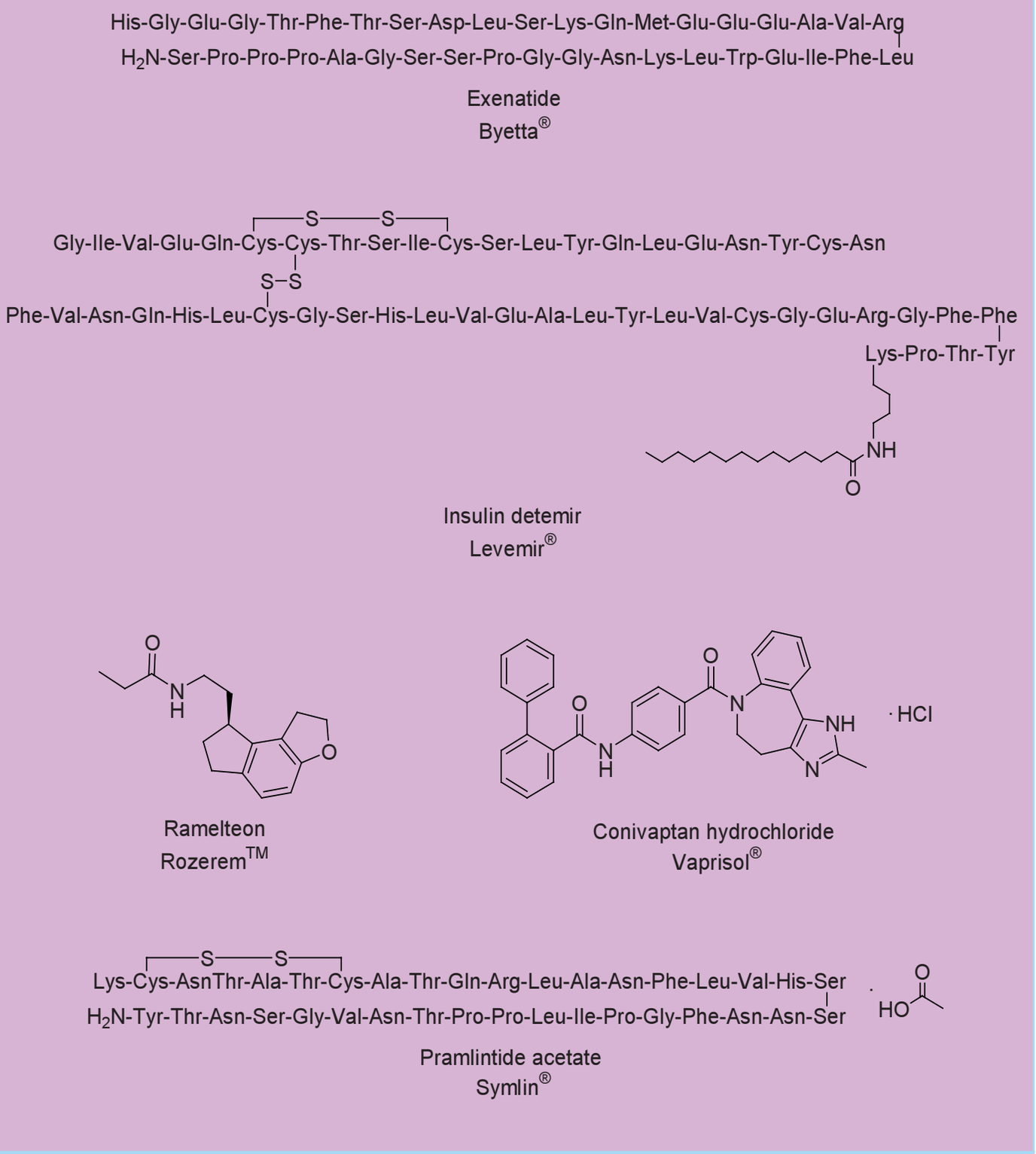

Fig. 5 - NME approved by “standard review”

metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.
Date Approved: 28-04-2005

Levemir® (Novo Nordisk)
Insulin detemir, 10 U/mL, injection
Indication: long-acting insulin analogue for once or twice-daily subcutaneous administration to treat type 1 or type 2 diabetes in adults requiring basal (long-acting) insulin for control of hyperglycemia.
Date Approved: 16-06-2005 (available also in Italy [25])

Rozerem™ (Takeda)
Ramelteon, 8 mg, tablet
Indication: melatonin MT_1/MT_2 receptor agonist for treatment of insomnia characterized by difficulty with sleep onset.
Date Approved: 22-07-2005

Symlin® (Amlyn)
Pramlintide acetate, 0.6 mg/mL, injection
Indication: synthetic human amylin for use as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy for type 1 diabetes and for type 2 diabetes with or without a concurrent sulfonylurea agent and/or metformin.
Date Approved: 16-03-2005

Vaprisol® (Astellas)
Conivaptan hydrochloride, 20 mg, injection
Indication: dual V_{1a}/V_2 vasopressin receptor antagonist for treatment of euvolemic hyponatremia in hospitalized patients
Date Approved: 29-12-2005

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